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EXAMINER

BERTOGLIO, VALARIE E

ART UNIT PAPER NUMBER

1632

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/045,018

Applicant(s)

MITRANI, EDUARDO N.

Examiner

Valarie Bertoglio

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 November 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) 1-17 and 28-33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01/15/2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>09/01/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response dated 11/15/2004 has been entered. Claims 18 and 28 have been amended. Claims 1-33 are pending. Claims 18-28 are under current consideration.

Election/Restrictions

Claims 1-17 and 29-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/19/2004.

Specification

The objection to the specification is withdrawn in light of Applicant's amendment to the specification.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 23 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for repopulating a devitalized acellular three dimensional scaffold with pluripotent stem cells or progenitor cells derived from the same tissue source as the scaffold, does not reasonably provide enablement for repopulating the scaffold with any differentiated cell type. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant's arguments set forth on pages 8-11 of the response filed 11/15/2004 have been fully considered and are found partially persuasive. The aspect of the rejection regarding the use of synthetic scaffolds is withdrawn in light of the amendment to the claims requiring a devitalized scaffold. The aspect of the rejection regarding repopulating the scaffold with differentiated, as opposed to pluripotent cells, is maintained for claims 18,23 and 25-27 for reasons of record set forth on pages 4-5 of the previous office action.

Applicant has provided evidence regarding the state of the art with regard to transdifferentiation and dedifferentiation of differentiated cells, establishing that differentiated cells can either change fate or dedifferentiate and be directed along a different fate path when subjected to specific conditions. Applicant has also argued that this transdifferentiation and dedifferentiation process is not necessary for differentiated cells to proliferate and grow on the claimed scaffold. Applicant states that cells such as chondrocytes are capable of maintaining functions characteristic to the organs from which they originate (see Applicant's response at page 10, paragraph 3).

In response, while pluripotent stem cells may not be the only enabled embodiment of the claims, the specification is still deemed to not be fully enabling for the full scope of the claimed invention. Applicant has set forth that differentiated cells can be used to repopulate the scaffolds as they are capable of maintaining functions characteristic to the organs from which they originate. This would hold true when differentiated cells are used to populate scaffolds originating from the same tissue type as the differentiated cells. What is not enabled is heterologous differentiated cell types, i.e. using differentiated cells from the retina to repopulate a scaffold generated from liver. It cannot be predicted what would happen to these

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cells. It is not known what fate the cells may take on, whether they live, die or proliferate.

Thus, one of ordinary skill in the art would not know how to use such a scaffold because if it were to be repopulated by the once retinal cells, the artisan cannot predict without undue experimentation, what the cells repopulating the scaffold would be. While dedifferentiation and transdifferentiation is known in the art to occur using specific culture conditions, how to do so in repopulating a devitalized acellular scaffold derived from an organ wherein the extracellular nature and characteristics of the organ are maintained and active, is not known in the art and is not taught by the instant specification. Therefore, the claims should be narrowed in scope to encompass either pluripotent stem cells that are known to be capable of taking on multiple cell fates based on varying extracellular cues such as those of a microorganism or narrowed to encompass only differentiated cells from the organ from which the scaffold originates.

Therefore, in light of the breadth of the claims including repopulating a devitalized acellular scaffold with differentiated heterologous cells and in light of the lack of guidance in the specification regarding repopulation of the scaffold with differentiated cells, it would require undue experimentation for one of ordinary skill in the art to carry out the full scope of the invention as claimed.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 18-28 under the second paragraph of 35 U.S.C. 112 is withdrawn in light of Applicant's arguments and amendments to the claims. Applicant has pointed to a more clear definition of microorganism in the specification at page 18, lines 17-21 and

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has amended claim 18 to overcome the aspect of the rejection relating to the lack of clarity of the term "repopulate".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) The rejection of claims 18-28 under 35 U.S.C. 102(b) as being anticipated by Vacanti (1999) is maintained for reasons of record advanced on pages 6-7 of the previous office action. Applicant's arguments set forth on pages 13-14 of Applicant's response have been fully considered and are not found persuasive.

Applicant has amended claim 18 adding the requirement that the scaffold be devitalized. The specification at page 32 sets forth that a devitalized scaffold is one which all of the cellular mass is removed.

The scaffold of Vacanti is devitalized as it is free of cells. The limitation of devitalized fails to differentiate the claimed structure from that of Vacanti. The limitation imposed by the term "devitalized", at best, imparts limitation on the process by which the scaffold used in the claimed method is obtained. Because the scaffold of Vacanti (1999) meets the structural limitations of the scaffold used in the claimed methods and because Vacanti (1999) meets the other limitations of the claims as set forth in the previous office action, Vacanti (1999) meets all of the limitations of claims 18-24.

2) The rejection of claim 18 under 35 U.S.C. 102(b) as being anticipated by Vacanti (1998) is maintained for reasons of record advanced on page 8 of the previous office action. Applicant's arguments set forth on pages 13-14 of Applicant's response have been fully considered and are not found persuasive.

Applicant has amended claim 18 adding the requirement that the scaffold be devitalized. The specification at page 32 sets forth that a devitalized scaffold is one which all of the cellular mass is removed.

The scaffold of Vacanti is devitalized as it is free of cells. The limitation of devitalized fails to differentiate the claimed structure from that of Vacanti. The limitation imposed by the term "devitalized", at best, imparts limitation on the process by which the scaffold used in the claimed method is obtained. Because the scaffold of Vacanti (1998) meets the structural limitations of the scaffold used in the claimed method, Vacanti (1998) meets all of the limitations of claim 18.

3) The rejection of claims 18-20 and 22-28 under 35 U.S.C. 102(b) as being anticipated by Riviere is maintained. Applicant's arguments set forth on pages 14-15 of Applicant's response have been fully considered and are not found persuasive.

Applicant has argued that the claims now require that the scaffold be devitalized and acellular. Applicant has further presented evidence in support of the fact that irradiated bone marrow is not acellular as it contains living cells even after doses of radiation that kill many but not all bone marrow cells.

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In response, the art demonstrates that devitalized, acellular scaffolds made from tissue explants are not completely void of cells. For example, Mitchell (US2002/0115208) taught that in decellularizing tissues to be used as a scaffold, not 100% decellularization occurs and that obtaining such a degree of decellularization would be at the expense of desirable characteristics of the scaffold (see paragraph 0111). Therefore, because the specification does not define a devitalized acellular scaffold as being 100% void of cells, the teachings of Riviere fulfill the limitations of the claims to the extent that the bone marrow is substantially decellularized and therefore devitalized.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

1) The rejection of claims 18-24 under 35 U.S.C. 103(a) as being unpatentable over Mitchell in view of Vacanti ('417) and Vacanti ('610) is maintained for reason of record set forth on pages 10-11 of the previous office action.

Applicant has argued that the person of ordinary skill in the art would not be motivated to apply the dimensions for a synthetic scaffold taught by Vacanti to a devitalized acellular scaffold derived from a tissue explant (see paragraph bridging pages 15-16 of Applicant's response). Applicant argues that a number of US patents teaching methods of decellularizing tissue that also reference Vacanti are silent with respect to the scaffold dimensions. Applicant

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asserts that this silence is indicative of nonobviousness. Applicant also teaches that Mitchell discloses culturing muscle cells on a 2-3 centimeter segment of decellularized artery and that one cannot assume that Mitchell would have desired to use the size limitations taught by Vacanti.

In response, being 2-3 cm in length does not prohibit control of the tissue dimensions such that the cells positioned deepest within a scaffold are not more than 225 micrometers from the cells nearest the surface as required by the claims. Mitchell does not disregard the teachings of Vacanti as stated by Applicant. The example of vascular tissue taught by Mitchell is not subject to the limits of diffusion as taught by Vacanti as the cells remain on the surface (see paragraph 0170). Diffusion of oxygen and nutrients to the cells is not an issue for this scaffold. The teachings of Mitchell are not limited to this vascular explant. It would be obvious based on the teaching of Mitchell to generate artificial tissue explants using other tissue scaffolds that would be affected by the limits of diffusion as taught by Vacanti. Vacanti taught that a problem inherent in scaffolds is that the cells in the interior of a thick matrix fail to receive nutrients and gases through diffusion. The teachings of Vacanti provide motivation to alter the teachings of Mitchell to allow for better survival of cells on the inner surfaces of the scaffold. Mitchell and Vacanti together provided the teachings that make the claimed invention obvious and Vacanti provides the motivation to use the claimed dimensions. The teachings of Mitchell fail to discount those of Vacanti.

2)The rejection of claims 18 and 23-26 under 35 U.S.C. 103(a) as being unpatentable over Bruchman in view of Vacanti ('417) and Vacanti ('610) is maintained for reason of record set forth on pages 11-12 of the previous office action.

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Applicant has argued that one of ordinary skill in possession of the teachings of Bruchman would not be motivated to combine the teachings of Vacanti to generate tissues from devitalized explants with the claimed size limitations.

In response, as set forth above and in the previous office action, Vacanti taught that survival of cells in the middle of a thick explant fail to survive due to the limits of diffusion of nutrients and gases. The skilled artisan would be motivated to combine the teachings of Bruchman and of Vacanti to generate the claimed scaffold that allowed cells repopulating a scaffold to be within limits of diffusion to exchange nutrients and waste.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Joe Wauters
AU1632